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(71) Applicant (for all designated States except US): NEUROSEARCH A/S [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PETERS, Dan** [SE/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **OLSEN, Gunnar, M.** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **NIELSEN, Elsebet, Østergaard** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **JØRGENSEN, Tino, Dyhring** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **AHRING, Philip, K.** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(74) Common Representative: NEUROSEARCH A/S; Att: Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).

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(54) Title: NOVEL DIAZABICYCLIC BIARYL DERIVATIVES

(57) Abstract: This invention relates to novel diazabicyclic biaryl derivatives, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors and modulators of the monoamine receptors and transporters. Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

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NOVEL DIAZABICYCLIC BIARYL DERIVATIVES

TECHNICAL FIELD

5 This invention relates to novel diazabicyclic biaryl derivatives, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors and modulators of the monoamine receptors and transporters.

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the
10 cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

15

BACKGROUND ART

The endogenous cholinergic neurotransmitter, acetylcholine, exert its biological effect via two types of cholinergic receptors, the muscarinic Acetyl Choline
20 Receptors (mAChR) and the nicotinic Acetyl Choline Receptors (nAChR).

As it is well established that muscarinic acetylcholine receptors dominate quantitatively over nicotinic acetylcholine receptors in the brain area important to memory and cognition, and much research aimed at the development of agents for the treatment of memory related disorders have focused on the synthesis of muscarinic
25 acetylcholine receptor modulators.

Recently, however, an interest in the development of nAChR modulators has emerged. Several diseases are associated with degeneration of the cholinergic system i.e. senile dementia of the Alzheimer type, vascular dementia and cognitive impairment due to the organic brain damage disease related directly to alcoholism.
30 Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency.

US 5478939 (American Cyanamid) and WO 00/34284 (Sanofi-Synthelabo) both describe 2,5-diazabicyclo[2.2.1]heptane derivatives having affinity for nicotinic receptors. WO 00/44755 (Abbott) describes diazabicyclic derivatives useful as
35 nicotinic acetylcholine receptor ligands, incl. certain 2,5-diazabicyclo[2.2.1]heptane derivatives. However, the 2,5-diazabicyclo-[2.2.1]-heptane of the present invention have not been disclosed.

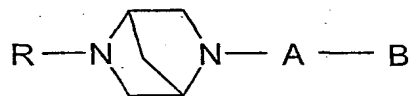
SUMMARY OF THE INVENTION

The present invention is devoted to the provision novel modulators of the nicotinic and/or of the monoamine receptors, which modulators are useful for the treatment of diseases or disorders related to the cholinergic receptors, and in particular the nicotinic acetylcholine receptor (nAChR), the serotonin receptor (5-HT₁), the dopamine receptor (DAR) and the norepinephrine receptor (NER), and of the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and norepinephrine (NE).

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

The compounds of the invention may also be useful as diagnostic tools or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging), and they may be used in labelled or unlabelled form.

In its first aspect the invention provides novel (R,R) or (S,S) diazabicyclic biaryl derivative represented by Formula I



or an enantiomer or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an aza-onium salt thereof, wherein

R represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl or benzyl; and

A represents a phenylene group, or a 5- or 6-membered aromatic monocyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro; and

B represents

an aromatic monocyclic or bicyclic carbocyclic group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro;

a 5- or 6-membered aromatic monocyclic heterocyclic group, which monocyclic heterocyclic group may optionally be substituted one or more times with

substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro; or

an aromatic bicyclic heterocyclic group, which bicyclic heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro;

provided however, if A represents 2,5-pyridyl or 3,6-pyridazinyl, then B is not phenyl or substituted phenyl.

In its second aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the diazabicyclic biaryl derivative of the invention, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

In a further aspect the invention relates to the use of the diazabicyclic biaryl derivative of the invention, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors.

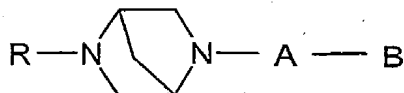
In a final aspect the invention provides methods of treatment, prevention or alleviation of diseases, disorders or conditions of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of the diazabicyclic biaryl derivative of the invention.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

30 Diazabicyclic Biaryl Derivative

In a first aspect, novel diazabicyclic biaryl derivatives are provided. The diazabicyclic biaryl derivatives of the invention are (R,R) or (S,S) 2,5-diazabicyclo-[2.2.1]-heptane biaryl derivatives represented by the general Formula I:



or an enantiomer or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an aza-onium salt thereof, wherein

R represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl or benzyl; and

A represents a phenylene group, or a 5- or 6-membered aromatic monocyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro; and

B represents

an aromatic monocyclic or bicyclic carbocyclic group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro;

a 5- or 6-membered aromatic monocyclic heterocyclic group, which monocyclic heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro; or

an aromatic bicyclic heterocyclic group, which bicyclic heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro;

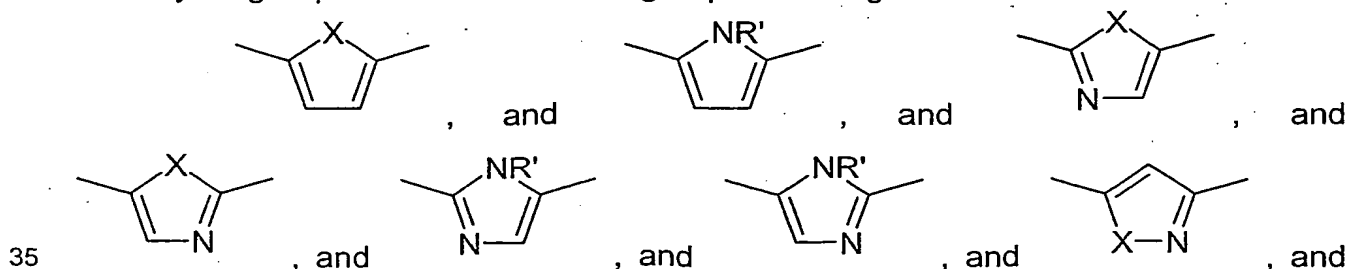
provided however, if A represents 2,5-pyridyl or 3,6-pyridazinyl, then B is not phenyl or substituted phenyl.

In a 1st preferred embodiment R represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl.

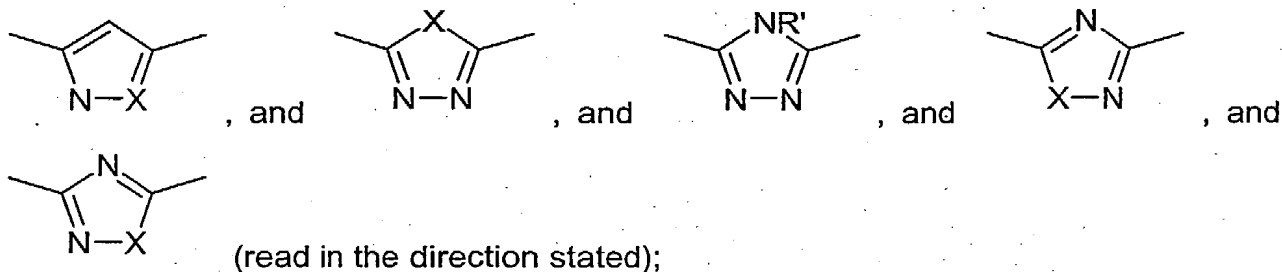
In a 2nd preferred embodiment A represents *m*-phenylene or *p*-phenylene, which phenylene group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro.

In a more preferred embodiment A represents a 5-membered aromatic monocyclic heterocyclic group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro.

In a yet more preferred embodiment the 5-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:



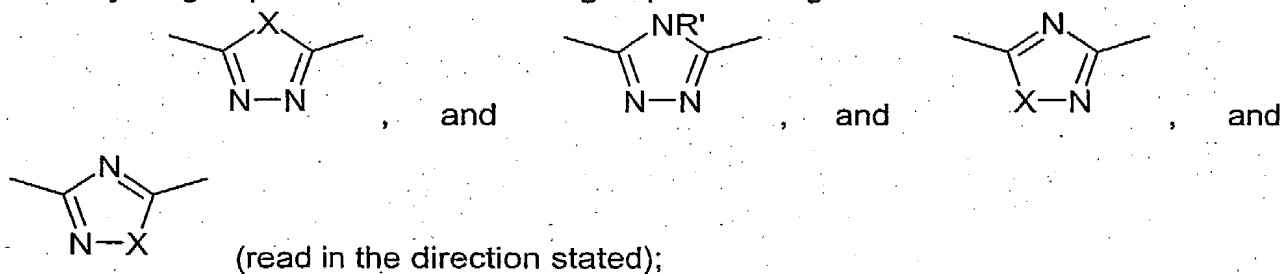
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wherein X represents O, S or Se; and

R' represents hydrogen or alkyl.

15 In a still more preferred embodiment the 5-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:

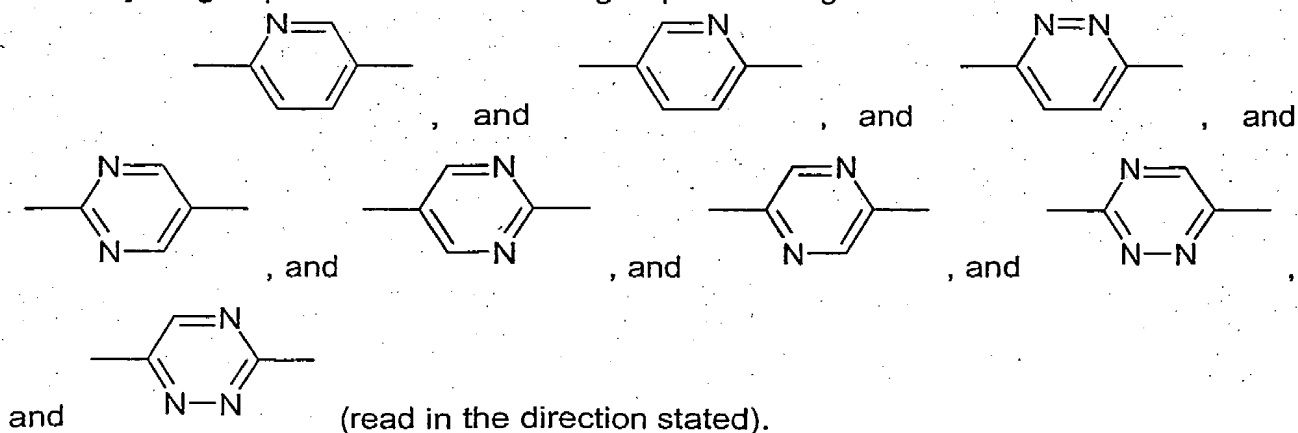


wherein X represents O or S; and

R' represents hydrogen or alkyl.

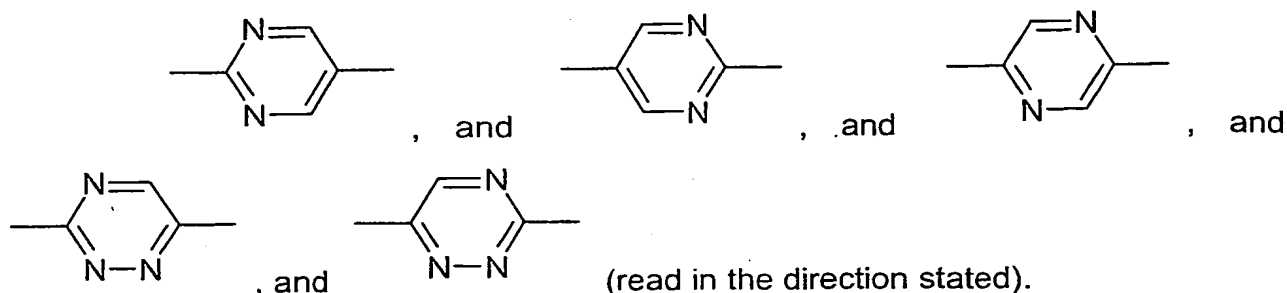
10 In a 3rd preferred embodiment A represents a 6-membered aromatic monocyclic heterocyclic group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro.

15 In a more preferred embodiment 6-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:

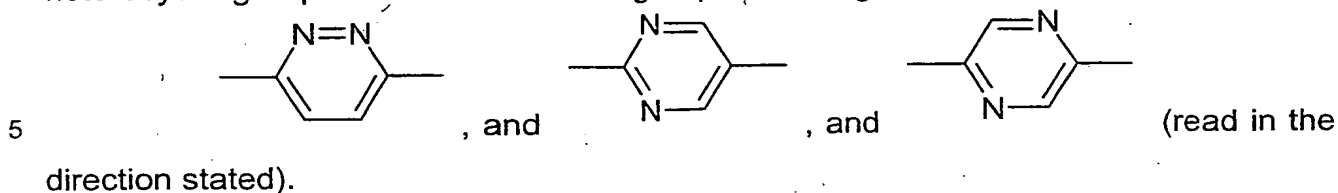


20 In an even more preferred embodiment 6-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:

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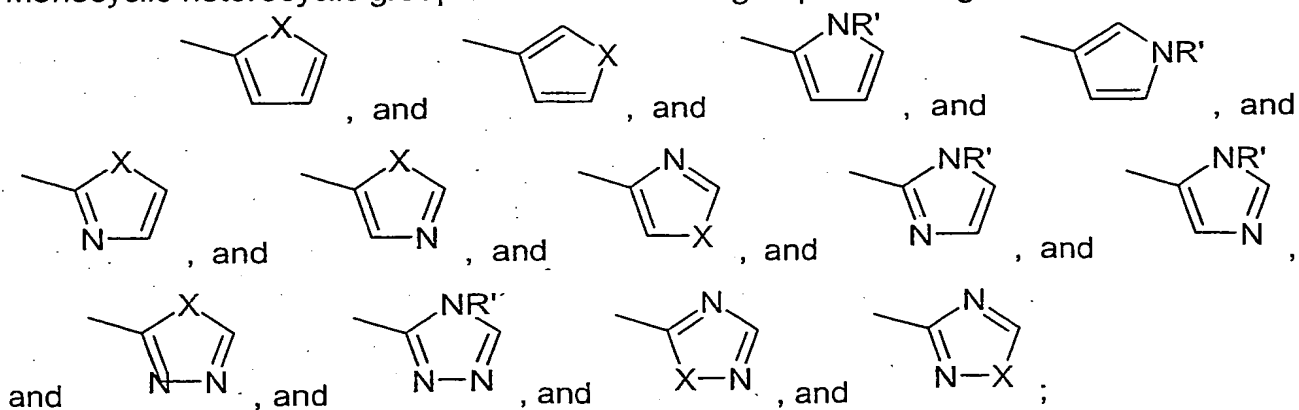
In a still more preferred embodiment the 6-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:



In a 4th preferred embodiment B represents a phenyl or naphthyl group, which aryl group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, 10 CF₃, OCF₃, CN, amino and nitro.

In a 5th preferred embodiment B represents a 5- or 6-membered aromatic monocyclic heterocyclic group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro.

In a more preferred embodiment the B represents a 5-membered aromatic monocyclic heterocyclic group selected from the group consisting of:

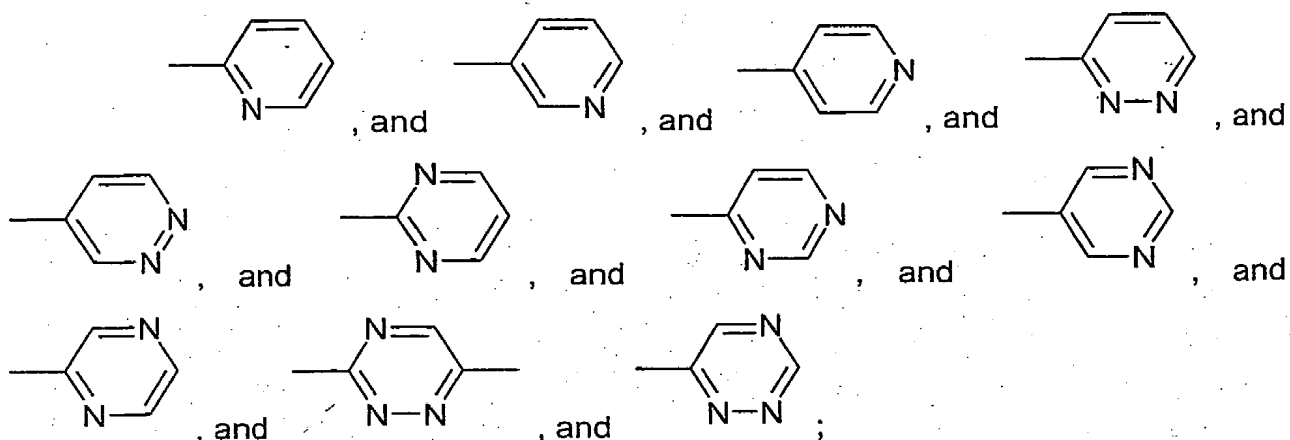


wherein X represents O, S or Se;

R' represents hydrogen or alkyl;

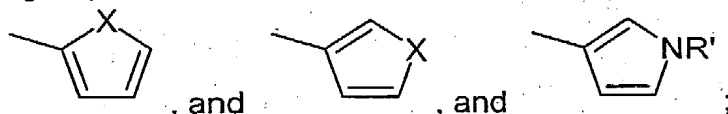
which aromatic group may optionally be substituted as specified above;

or B represents a 6-membered aromatic monocyclic heterocyclic group selected from the group consisting of:



which aromatic group may optionally be substituted as specified above.

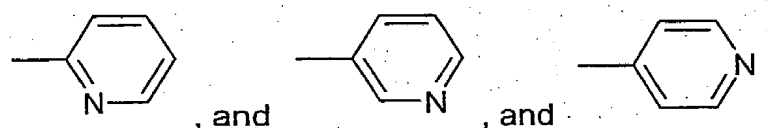
- 5 In a more preferred embodiment the 5-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:



wherein X represents O or S;

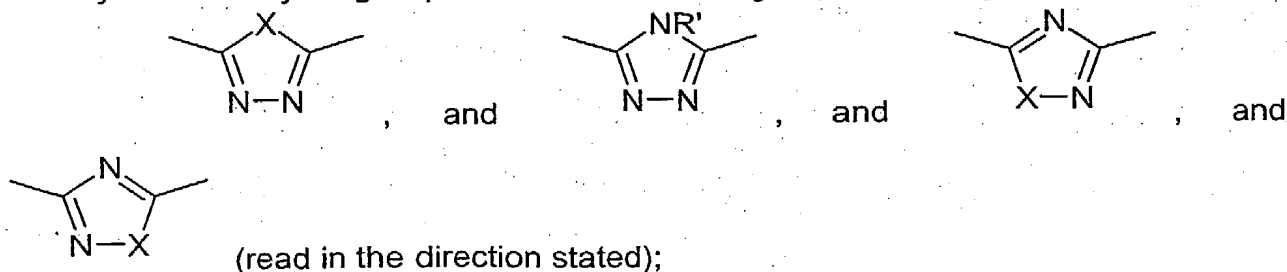
R' represents hydrogen or alkyl;

- 10 which aromatic group may optionally be substituted as specified above;
and the 6-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:



which aromatic group may optionally be substituted as specified above.

- 15 In a 6th preferred embodiment A represents a 5-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:

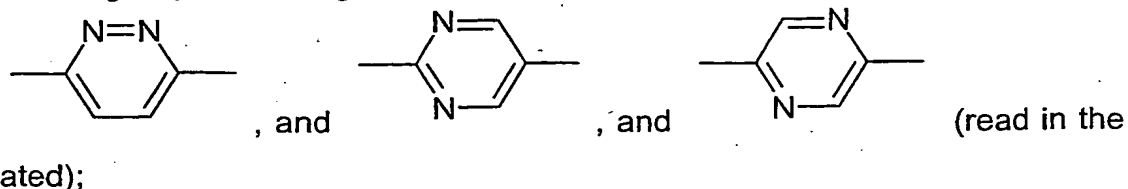


wherein X represents O or S; and

R' represents hydrogen or alkyl;

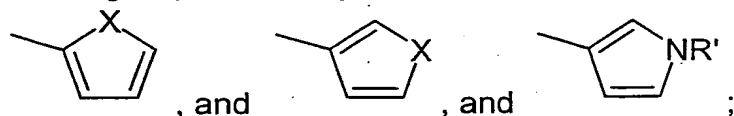
- 20 which aromatic group is optionally substituted with a substituent selected from the group consisting of halogen, CF₃, CN, amino and nitro;

or A represents a 6-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:



5 which aromatic group is optionally substituted with a substituent selected from the group consisting of halogen, CF₃, CN, amino and nitro;

and B represents a 5-membered aromatic monocyclic heterocyclic group selected from the group consisting of:



10 wherein X represents O or S; and

R' represents hydrogen or methyl;

which aromatic group may optionally be substituted one or two times with substituents selected from the group consisting of halogen, CF₃, CN, amino and nitro.

In a most preferred embodiment the diazabicyclic biaryl derivative of the invention is

2-[6-(3-Thienyl)-3-pyridazinyl]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;

5-Methyl-2-[6-(3-thienyl)-3-pyridazinyl]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-

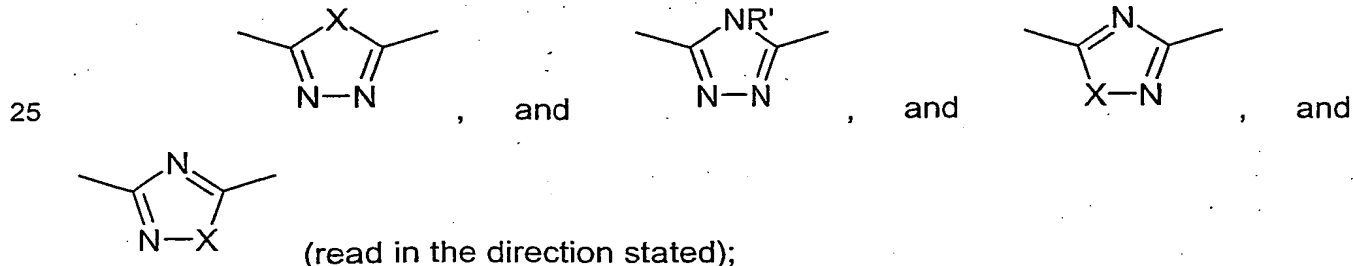
heptane; or

2-[6-(3-Thienyl)-2-pyrazinyl]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;

20 or an enantiomer or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

In a 7th preferred embodiment

A represents a 5-membered aromatic monocyclic heterocyclic group is selected from the group consisting of:



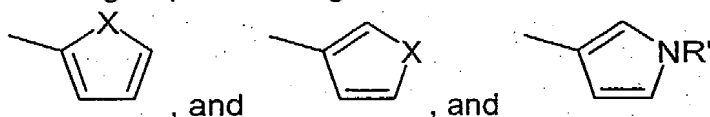
wherein X represents O or S;

R' represents hydrogen or alkyl; and

B represents a phenyl or naphthyl group;

which phenyl or naphthyl group may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro; or

B represents a 5-membered aromatic monocyclic heterocyclic group
5 selected from the group consisting of:



wherein X represents O or S; and

R' represents hydrogen or methyl;

which aromatic group may optionally be substituted one or two times with
10 substituents selected from the group consisting of halogen, CF₃, CN, amino and nitro.

In a most preferred embodiment the diazabicyclic biaryl derivative of the invention is

2-[2-(-5-Phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;

2-[5-(-3-Phenyl-1,2,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;

15 5-Methyl-2-[2-(-5-phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;

5-Methyl-2-[5-(-3-phenyl-1,2,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane; or

20 5,5-Dimethyl-2-[2-(-5-phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;

or an enantiomer or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

Definition of Substituents

25 In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom. Thus, a trihalogenmethyl group represents e.g. a trifluoromethyl group, a trichloromethyl group and similar trihalogen-substituted methyl groups.

In the context of this invention an alkyl group designates a univalent
30 saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C₁₋₁₈-alkyl), more preferred of from one to six carbon atoms (C₁₋₆-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C₁₋₄-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another
35 preferred embodiment of this invention alkyl represents a C₁₋₃-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention an alkenyl group designates a straight or branched carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to eight carbon atoms (C_{2-8} -alkenyl), more preferred of from two to six carbon atoms (C_{2-6} -alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl (allyl); 1-, 2- or 3-butenyl, or 1,3-butadienyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexadienyl, or 1,3,5-hexatrienyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-octenyl, or 1,3-octadienyl, or 1,3,5-octatrienyl, or 1,3,5,7-octtetraenyl.

10 In the context of this invention an alkynyl group designates a straight or branched carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to eight carbon atoms (C_{2-8} -alkynyl), more preferred of from two to six carbon atoms (C_{2-6} -alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butylnyl, or 1,3-butadiynyl; 1-, 2-, 3-, 4-pentylnyl, or 1,3-pentadiynyl; 1-, 2-, 3-, 4-, or 5-henylnyl, or 1,3-hexadiynyl or 1,3,5-hexatriynyl; 1-, 2-, 3-, 4-, 5- or 6-heptynyl, or 1,3-heptadiynyl, or 1,3,5-hepttriynyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-octynyl, or 1,3-octdiynyl, or 1,3,5-octtriynyl, or 1,3,5,7-octtetraynyl.

20 In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7} -cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy groups of the invention include methoxy and ethoxy.

30 In the context of this invention an aromatic mono- or bicyclic carbocyclic group is a mono- or bi-cyclic carbocyclic group holding carbon only as ring atom (i.e. mono- or bi-cyclic aryl groups). Examples of preferred aromatic mono- and bi-cyclic carbocyclic groups of the invention include phenyl, indenyl, naphthyl, azulenyl, fluorenyl, and anthracenyl. In a most preferred embodiment an aryl group of the invention is phenyl.

In the context of this invention an aromatic monocyclic heterocyclic group designates a heteroaryl group, which holds one or more heteroatoms in its ring structure. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S).

Preferred aromatic monocyclic heteroaryl groups of the invention include aromatic 5- and 6 membered heterocyclic monocyclic groups.

Examples of preferred aromatic heterocyclic monocyclic 5-membered groups of the invention include furanyl, in particular 2- or 3-furyl; thienyl, in particular 2- or 3-thienyl; pyrrolyl, in particular 1-, 2- or 3-pyrrolyl; oxazolyl, in particular oxazol-(2-, 4- or 5-)yl; thiazolyl, in particular thiazol-(2-, 4-, or 5-)yl; imidazole, in particular imidazol-(1-, 2-, 4- or 5-)yl; pyrazole, in particular pyrazol-(1-, 3-, 4- or 5-)yl; isoxazole, in particular isoxazol-(3-, 4- or 5-)yl; isothiazole, in particular isothiazol-(3-, 4- or 5-)yl; 1,2,3-oxadiazole, in particular 1,2,3-oxadiazol-(4- or 5-)yl; 1,2,4-oxadiazole, in particular 1,2,4-oxadiazol-(3- or 5-)yl; 1,2,5-oxadiazole, in particular 1,2,5-oxadiazol-(3- or 4-)yl; 1,3,4-oxadiazole, in particular 1,3,4-oxadiazol-(2- or 5-)yl; 1,2,3-triazole, in particular 1,2,3-triazol-(1-, 4- or 5-)yl; 1,2,4-triazole, in particular 1,2,4-triazol(1-, 3- or 4-)yl; 1,2,4-thiadiazole, in particular 1,2,4-thiadiazol-(3- or 5-)yl; 1,2,5-thiadiazole, in particular 1,2,5-thiadiazol-(3- or 4-)yl; 1,3,4-thiadiazole, in particular 1,3,4-thiadiazol-(2- or 5-)yl; and tetrazole, in particular tetrazol-(1- or 5-)yl.

Examples of preferred aromatic heterocyclic monocyclic 6-membered groups of the invention include pyridine, in particular pyridin-(2-,3- or 4-)yl; pyridazine, in particular pyridazin-(3- or 4-)yl; pyrimidine, in particular pyrimidin-(2-,4- or 5-)yl; pyrazine, in particular pyrazin-(2-,3-,5- or 6-)yl; 1,3,5-triazine, in particular 1,3,5-triazin-(2-,4- or 6-)yl; and phosphinine, in particular phosphinin-(2-,3- or 4-)yl.

In the context of this invention the term "aromatic bicyclic heterocyclic group" includes benzo-fused five- and six-membered heterocyclic rings containing one or more heteroatoms. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S).

Preferred aromatic bicyclic heteroaryl groups of the invention include indoliziny, in particular 2,5 or 6-indoliziny; indolyl, in particular 2,5 or 6-indolyl; isoindolyl, in particular 2,5 or 6-isoindolyl; benzo[b]furanyl, in particular 2,5 or 6-benzofuranyl; benzo[b]thienyl, in particular 2,5 or 6-benzothieryl; benzoimidazolyl, in particular 2,5 or 6-benzoimidazolyl; benzothiazolyl, in particular 5 or 6-benzothiazolyl; purinyl, in particular 2 or 8-purinyl; quinolinyl, in particular 2,3,6 or 7-quinolinyl; isoquinolinyl, in particular 3,6 or 7-isoquinolinyl; cinnolinyl, in particular 6 or 7-cinnolinyl; phthalazinyl, in particular 6 or 7-phthalazinyl; quinazolinyl, in particular 2,6 or 7-quinazolinyl; quinoxalinyl, in particular 2 or 6-quinoxalinyl; 1,8-naphthyridinyl, in particular 1,8-naphthyridin-2,3,6 or 7-yl; and pteridinyl, in particular 2,6 or 7-pteridinyl.

Pharmaceutically Acceptable Salts

The diazabicyclic biaryl derivative of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically

(i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Metal salts of a chemical compound of the invention include alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts (aza-onium salts). Preferred aza-onium salts include the alkyl-onium salts, in particular the methyl- and the ethyl-onium salts; the cycloalkyl-onium salts, in particular the cyclopropyl-onium salts; and the cycloalkylalkyl-onium salts, in particular the cyclopropyl-methyl-onium salts. The most preferred aza-onium salts of the invention are the methyl- and the ethyl-onium salts.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived

from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

10 **Methods of Producing Diazabicyclic Biaryl Derivatives**

The diazabicyclic biaryl derivative of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

The present invention relates to novel azacyclic ethynyl derivatives, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors (nAChR), and modulators of the monoamine receptors, in particular the biogenic amine transporters such as the serotonin receptor (5-HT₁), the dopamine receptor (DAR) and the norepinephrine receptor (NER), and of the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and norepinephrine (NE). Also preferred azacyclic ethynyl derivatives of the invention show selective α_7 activity. The compounds of the present invention may in particular be agonists, partial agonists, antagonists and allosteric modulators of the receptor.

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases, PNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neuro-degeneration, diseases related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

In a preferred embodiment the compounds of the invention are used for the treatment of diseases, disorders, or conditions relating to the central nervous system.

Such diseases or disorders includes anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, psychosis, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

In a preferred embodiment diseases, disorders, or conditions relating to the central nervous system for which the compounds of the invention are used are cognitive disorders, psychosis, schizophrenia and/or depression.

In another preferred embodiment the compounds of the invention may be useful for the treatment of diseases, disorders, or conditions associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

In yet another preferred embodiment the compounds of the invention may be useful for the treatment of endocrine disorders, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

In still another preferred embodiment the compounds of the invention may be useful for the treatment of neurodegenerative disorders, including transient anoxia and induced neuro-degeneration.

In even another preferred embodiment the compounds of the invention may be useful for the treatment of inflammatory diseases, disorders, or conditions, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

In still another preferred embodiment the compounds of the invention may be useful for the treatment of mild, moderate or even severe pain of acute, chronic or recurrent character, as well as pain caused by migraine, postoperative pain, and phantom limb pain.

Finally the compounds of the invention may be useful for the treatment of withdrawal symptoms caused by termination of use of addictive substances. Such addictive substances include nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol. Withdrawal from addictive substances is in general a traumatic experience characterised by anxiety and frustration, anger, anxiety, difficulties in

concentrating, restlessness, decreased heart rate and increased appetite and weight gain.

In this context "treatment" covers treatment, prevention, prophylactics and alleviation of withdrawal symptoms and abstinence as well as treatment resulting in a voluntary diminished intake of the addictive substance.

In another aspect, the compounds of the invention are used as diagnostic agents, e.g. for the identification and localisation of nicotinic receptors in various tissues.

10 Neuroimaging

The diazabicyclic biaryl derivatives of the invention may be useful as diagnostic tools or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging).

In another aspect of the invention, a method for the non-invasive determination of the distribution of a tracer compound inside a whole, intact living animal or human body using a physical detection method is provided. According to this method a tracer compound is a compound of the invention, or any of its enantiomers or any mixture thereof, an N oxide thereof, a pharmaceutically acceptable salt thereof, in a labelled or un-labelled form.

In a preferred embodiment the physical detection method is selected from PET, SPECT; MRS, MRI, CAT, or combinations thereof.

The labelled compound of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}O , ^{13}N , ^{123}I , ^{125}I , ^{131}I , ^{18}F and $^{99\text{m}}\text{Tc}$.

An example of commercially available labelling agents, which can be used in the preparation of the labelled compounds of the present invention is $[^{11}\text{C}]\text{O}_2$, ^{18}F , and NaI with different isotopes of Iodine.

In particular $[^{11}\text{C}]\text{O}_2$ may be converted to a $[^{11}\text{C}]$ -methylating agent, such as $[^{11}\text{C}]\text{H}_3\text{I}$ or $[^{11}\text{C}]$ -methyl triflate.

The tracer compound can be selected in accordance with the detection method chosen.

In one preferred embodiment, the labelled or unlabelled compound of the invention can be detected by a suitable spectroscopic method, in particular UV spectroscopy and/or fluorescence spectroscopy.

In another preferred embodiment, the compounds of the invention labelled by incorporation of an isotope into the molecule, which may in particular be an isotope of the naturally occurring atoms including ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}O ,

^{13}N , ^{123}I , ^{125}I , ^{131}I , ^{18}F and $^{99\text{m}}\text{Tc}$, and the isotope incorporation may be measured by conventional scintillation counting techniques.

In a third preferred embodiment, the physical method for detecting said tracer compound of the present invention is selected from Position Emission Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial X-ray Tomography (CAT), or combinations thereof.

Before conducting the method of the present invention, a diagnostically effective amount of a labelled or unlabelled compound of the invention is administered to a living body, including a human.

The diazabicyclic biaryl derivative of the invention is believed to be particularly suited for *in vivo* receptor imaging (neuroimaging).

In a particularly preferred embodiment the physical method for detecting the diazabicyclic biaryl derivative of the invention is Position Emission Tomography (PET).

It is currently believed that the diagnostically effective amount of the labelled or unlabelled compound of the invention, to be administered before conducting the *in vivo* method for the invention, is within a range of from 0.1 ng to 100 mg per kg body weight, preferably within a range of from 1 ng to 10 mg per kg body weight.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of diazabicyclic biaryl derivative of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the diazabicyclic biaryl derivative of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in

powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation.

- 5 When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

- 10 The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per
15 individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

- The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ p.o. The upper limit of the dosage range is presently considered
20 to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about 100 mg/kg/day p.o.

Methods of Therapy

- The diazabicyclic biaryl derivatives of the present invention are valuable
25 nicotinic and monoamine receptor modulators, and therefore useful for the treatment of a range of ailments involving cholinergic dysfunction as well as a range of disorders responsive to the action of nAChR modulators.

- In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal
30 body, including a human, which disease, disorder or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a diazabicyclic biaryl derivative of the invention.

- It is at present contemplated that suitable dosage ranges are 0.1 to 1000
35 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.005 mg/kg i.v. and 0.01 mg/kg p.o. The upper limit of the dosage range is about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.001 to about 1 mg/kg i.v. and from about 0.1 to about 10 mg/kg p.o.

5

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

10

Example 1

Preparatory Example

All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

2-[6-Bromo-3-pyridazinyl]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (Intermediate compound)

A mixture of *tert*-butyl-(1S,4S)-(+)-2,5-diazabicyclo-[2.2.1]-heptane-2-carboxylate (3.0 g, 15.1 mmol), 3,6-dibromopyridazine (3.6 g, 15.1 mmol) and dioxane (15 ml) was stirred for 3 days at 90°C. The crude product salt was filtered. Aqueous sodium hydroxide (50 ml, 1 M) was added to the solid material. The mixture was extracted with dichloromethane. Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 1.71 g (32%).

2-[6-(3-Thienyl)-3-pyridazinyl]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (Intermediate compound)

A mixture of 2-[6-bromo-3-pyridazinyl]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (1.65 g, 4.64 mmol), thiophene-3-boronic acid (0.89 g, 6.97 mmol), palladium acetate (42 mg, 0.19 mmol), tri-*tert*-butylphosphine (38 mg, 0.19 mmol), palladacycle (87 mg, 0.10 mmol), aqueous potassium carbonate (13.9 mmol, 2M), 1,3-propanediol (1.0 ml, 13.9 mmol) and dioxane (50 ml) was stirred at 100°C for eleven days. The mixture was evaporated, aqueous sodium hydroxide (50 ml, 1 M) was added and the mixture was extracted with ethyl acetate (3 x 50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 0.68 g (41%).

2-[6-(3-Thienyl)-3-pyridazinyl]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane fumaric acid salt (Compound 1A)

A mixture of 2-[6-(3-thienyl)-3-pyridazinyl]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (0.66 g, 1.84 mmol), trifluoroacetic acid (1.4 ml, 18.4 mmol) and dichloromethane (15 ml) was stirred for 15 hours. The mixture was evaporated and aqueous sodium hydroxide was added followed by extraction with dichloromethane (3 x 50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 0.35 g (73%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 162-165°C.

5-Methyl-2-[6-(3-thienyl)-3-pyridazinyl]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane (Compound 1B)

A mixture of 2-[6-(3-thienyl)-3-pyridazinyl]-(1S,4S)-(+)-2,5-diazabicyclo-[2.2.1]-heptane (0.21 g, 0.81 mmol), formic acid (0.92 ml, 24.4 mmol) and formaldehyde (0.68 ml, 24.4 mmol) was stirred at 100 °C for 6 hours. The mixture was evaporated. Aqueous sodium hydroxide (30 ml, 1 M) was added followed by extraction with ethyl acetate (3 x 30 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as an oil. Yield 0.15 g, 77%.

2-Chloro-5-phenyl-1,3,4-thiadiazole (Intermediate compound)

A mixture of 2-amino-5-phenyl-1,3,4-thiadiazole sulphate (10.0 g, 56.4 mmol) and conc. hydrochloric acid (100 ml) was stirred at 0°C. Sodium nitrite (5.06 g, 69 mmol) was added at 0°C. The mixture was stirred for 9 days at room temperature. The crystals were filtered and resuspended in aqueous hydrochloric acid (150 ml, 1M), stirred overnight and filtered. Aqueous sodium hydroxide (100 ml, 4 M) was added and extracted with ethyl acetate. Yield 5.68 g.

5-Chloro-3-phenyl-1,2,4-thiadiazole (Intermediate compound)

Was prepared in the same manner as 2-Chloro-5-phenyl-1,3,4-thiadiazole, from 5-amino-3-phenyl-1,2,4-thiadiazole.

2-[2(-5-Phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (Intermediate compound)

A mixture of *tert*-butyl-(1S,4S)-(+)-2,5-diazabicyclo-[2.2.1]-heptane-2-carboxylate (5.68 g, 28.6 mmol) and 2-chloro-5-phenyl-1,3,4-thiadiazole (5.63 g, 28.6 mmol) and dioxane (50 ml) was stirred at 100 °C for 10 days. Aqueous sodium hydroxide (100 ml, 1 M) was added and the mixture was extracted with ethyl acetate (3

x 100 ml). Chromatography on silica gel with ethyl acetate and petroleum (1 : 1) gave the title compound as an oil. Yield 5.52 g (54%).

2-[2-(-5-Phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane fumaric acid salt (Compound 1C)

A mixture of 2-[2-(5-phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (5.52 g, 15.4 mmol), trifluoroacetic acid (11.9 ml, 154 mmol) and dichloromethane (100 ml) was stirred for 15 hours. The mixture was evaporated, aqueous sodium hydroxide (100 ml, 1 M) was added and the mixture was extracted with dichloromethane (3 x 50 ml). The title compound was isolated in quantitative yield. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 187.5-196.7°C.

2-[5-(-3-Phenyl-1,2,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane fumaric acid salt (Compound 1D)

Was prepared from 2-[5-(3-phenyl-1,2,4-thiadiazolyl)]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane as described above. Mp 175.0-176.9°C.

5-Methyl-2-[2-(-5-phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane fumaric acid salt (Compound 1E)

A mixture of 2-[2-(5-phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane (2.0 g, 7.74 mmol), formic acid (25 ml, 98%) and formaldehyde (25 ml, 37%) was stirred at reflux for 15 hours. The mixture was evaporated, aqueous sodium hydroxide (100 ml, 1M) was added and extracted with dichloromethane (3 x 50 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 1.34 g (64%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp 200.4-206.0°C.

5-Methyl-2-[5-(-3-phenyl-1,2,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane fumaric acid salt (Compound 1F)

Was prepared from 2-[5-(3-phenyl-1,2,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane. Mp 128.9-129.2°C.

5,5-Dimethyl-2-[2-(-5-phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane iodide (Compound 1G)

Methyl iodide (105 µl, 1.69 mmol) in dichloromethane (5 ml) was added to a mixture of 5-methyl-2-[2-(5-phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-

[2.2.1]-heptane (0.46 g, 1.69 mmol) at -70°C over 10 minutes. The mixture was allowed to reach room temperature and filtered. Yield 0.42 g (60 %). Mp 250.3-255.1°C.

5 2-[6-Chloro-2-pyrazinyl]-(1S,4S)-5-tert-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (Intermediate compound)

A mixture of *tert*-butyl-(1S,4S)-(+)-2,5-diazabicyclo-[2.2.1]-heptane-2-carboxylate (10.0 g, 50.4 mmol), 2,6-dichloropyrazine (15.0 g, 101 mmol) and dioxane (100 ml) was stirred at 40°C for 3 days. The mixture was evaporated. Aqueous sodium hydroxide (100 ml, 1 M) was added, the mixture was evaporated to the half volume. The mixture was extracted with ethyl acetate (2 x 100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 11.6 g (73%).

15 2-[5-Bromo-6-chloro-2-pyrazinyl]-(1S,4S)-5-tert-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (Intermediate compound)

A mixture of 2-[6-chloro-2-pyrazinyl]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (10.6 g, 34.1 mmol), N-bromosuccinimide (6.06 g, 34.1 mmol) and acetonitrile (100 ml) was stirred for 3 hours. Aqueous sodium hydroxide (200 ml, 1 M) was added and the acetonitrile was evaporated. The mixture was extracted with ethyl acetate (2 x 200 ml). Chromatography on silica gel with ethyl acetate : petroleum (1:1) gave the title compound as free base. Yield 10.44 g (79%).

25 2-[5-(3-Thienyl)-2-pyrazinyl]-(1S,4S)-5-tert-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (Intermediate compound)

A mixture of 2-[5-bromo-6-chloro-2-pyrazinyl]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (4.0 g, 10.3 mmol), 3-thiophene boronic acid, aqueous potassium carbonate (15.4 ml, 2 M), 1,3-propandiol (2.34 g, 30.8 mmol), palladacycle (96 mg, 0.10 mmol), tri-*tert*-butylphosphine (83 mg, 0.41 mmol), palladium acetate (46 mg, 0.20 mmol) and dioxane (40 ml) was stirred at reflux for 5 days. Aqueous sodium hydroxide (50 ml, 1 M) was added and the mixture was extracted with ethyl acetate (2 x 30 ml). Chromatography on silica gel with ethyl acetate and petroleum (1:1) gave the title compound as an oil. Yield 1.46 g (41%). This single step also includes 6-dechlorination.

35 2-[5-(3-Thienyl)-2-pyrazinyl]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane fumaric acid salt (Compound 1H)

A mixture of 2-[5-(3-thienyl)-2-pyrazinyl]-(1S,4S)-5-*tert*-butoxycarbonyl-2,5-diazabicyclo-[2.2.1]-heptane (1.4 g, 3.9 mmol), trifluoroacetic acid (4.4 g, 39 mmol) was stirred for 15 hours. Aqueous sodium hydroxide (50 ml, 1 M) was added and the

mixture was extracted with dichloromethane (2 x 30 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound as free base. Yield 0.41 g (28%), Mp 208.4-208.9°C.

5 Example 2

***In vitro* Inhibition of ^3H - α -Bungarotoxine Binding in Rat Brain**

In this example the affinity of the compounds of the invention for binding to α_7 -subtype of nicotinic receptors is determined.

α -Bungarotoxine is a peptide isolated from the venom of the Elapidae snake *Bungarus multicinctus*. It has high affinity for neuronal and neuromuscular nicotinic receptors, where it acts as a potent antagonist.

^3H - α -Bungarotoxine labels nicotinic acetylcholine receptors formed by the α_7 subunit isoform found in brain and the α_1 isoform in the neuromuscular junction.

Tissue preparation

Preparations are performed at 0-4°C. Cerebral cortices from male Wistar rats (150-250 g) are homogenised for 10 seconds in 15 ml of 20 mM Hepes buffer containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM MgSO_4 and 2.5 mM CaCl_2 (pH 7.5) using an Ultra-Turrax homogeniser. The tissue suspension is subjected to centrifugation at 27,000 x g for 10 minutes. The supernatant is discarded and the pellet is washed twice by centrifugation at 27,000 x g for 10 minutes in 20 ml of fresh buffer, and the final pellet is then re-suspended in fresh buffer containing 0.01% BSA (35 ml per g of original tissue) and used for binding assays.

Assay

Aliquots of 500 μl of homogenate are added to 25 μl of test solution and 25 μl of ^3H - α -bungarotoxine (2 nM, final concentration) and mixed and incubated for 2 hours at 37°C. Non-specific binding is determined using (-)-nicotine (1 mM, final concentration). After incubation, the samples are added 5 ml of ice-cold Hepes buffer containing 0.05% PEI and poured directly onto Whatman GF/C glass fibre filters (pre-soaked in 0.1% PEI for at least 6 hours) under suction, and immediately washed with 2 x 5 ml ice-cold buffer.

The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

The test value is given as an IC_{50} (the concentration of the test substance which inhibits the specific binding of ^3H - α -bungarotoxin by 50%).

The results of these experiments are presented in Table 1 below.

Table 1Inhibition of ^3H - α -Bungarotoxine Binding

Compound No.	IC ₅₀ (μM)
1B	0.20
1H	0.26

Example 3***In vitro* Inhibition of ^3H -5-Hydroxytryptamine Uptake in Cortical Synaptosomes**

Serotonin transporters/uptake sites on nerve terminals presumably function to terminate neuronal signaling by removing serotonin from the synaptic cleft. The activity of the serotonin transporter integral protein can be measured *in vitro* by synaptosomal uptake of ^3H -5-hydroxytryptamine (5-HT, serotonin).

Preparations are performed at 0-4°C. Cerebral cortices from male Wistar rats (150-200 g) are homogenized for 5-10 seconds in 100 volumes of ice-cold 0.32 M sucrose containing 1 mM pargyline, using a motor driven teflon pestle in a glass homogenizing vessel. Monoamine oxidase activity is inhibited in the presence of pargyline.

The homogenate is subjected to centrifugation at 1000 x g for 10 minutes. The resulting supernatant is then centrifuged at 27,000 x g for 50 minutes and the supernatant is discarded. The pellet (P₂) is re-suspended in oxygenated (equilibrated with an atmosphere of 96% O₂: 4% CO₂ for at least 30 minutes) Krebs-Ringer incubation buffer (1000 ml per g of original tissue) at pH 7.2 containing 122 mM NaCl, 0.16 mM EDTA, 4.8 mM KCl, 12.7 mM Na₂HPO₄, 3.0 mM NaH₂PO₄, 1.2 mM MgSO₄, 1 mM CaCl₂, 10 mM glucose and 1 mM ascorbic acid.

Aliquots of 4.0 ml tissue suspension are added to 100 μl of test solution and 100 μl of ^3H -5-HT (1 nM, final concentration), mixed and incubated for 30 minutes at 37°C. Non-specific uptake is determined using Citalopram (1 μM , final concentration, available from Lundbeck, Denmark).

After incubation, the samples are poured directly onto Whatman GF/C glass fibre filters under suction. The filters are washed three times with 5 ml of ice-cold 0.9% (w/v) NaCl solution.

The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific uptake is calculated as the difference between total uptake and non-specific uptake.

25-75% inhibition of specific binding must be obtained, before calculation of an IC_{50} .

The test value is given as IC_{50} (the concentration (μM) of the test substance which inhibits the specific binding of 3H -5-HT by 50%).

5 The results are presented in Table 2 below.

Table 2

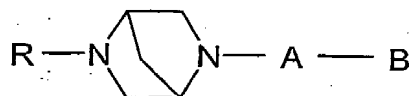
Inhibition of 3H -5-Hydroxytryptamine Uptake

Compound No.	IC_{50} (μM)
1A	0.51
1H	0.021

10

CLAIMS

1. A (R,R) or (S,S) diazabicyclic biaryl derivative represented by Formula I



- 5 or an enantiomer or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, or an aza-onium salt thereof, wherein

R represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl or benzyl; and

10

A represents a phenylene group, or a 5- or 6-membered aromatic monocyclic heterocyclic group, which heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro; and

15

B represents

an aromatic monocyclic or bicyclic carbocyclic group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro;

20

a 5- or 6-membered aromatic monocyclic heterocyclic group, which monocyclic heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro; or

25

an aromatic bicyclic heterocyclic group, which bicyclic heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro;

30

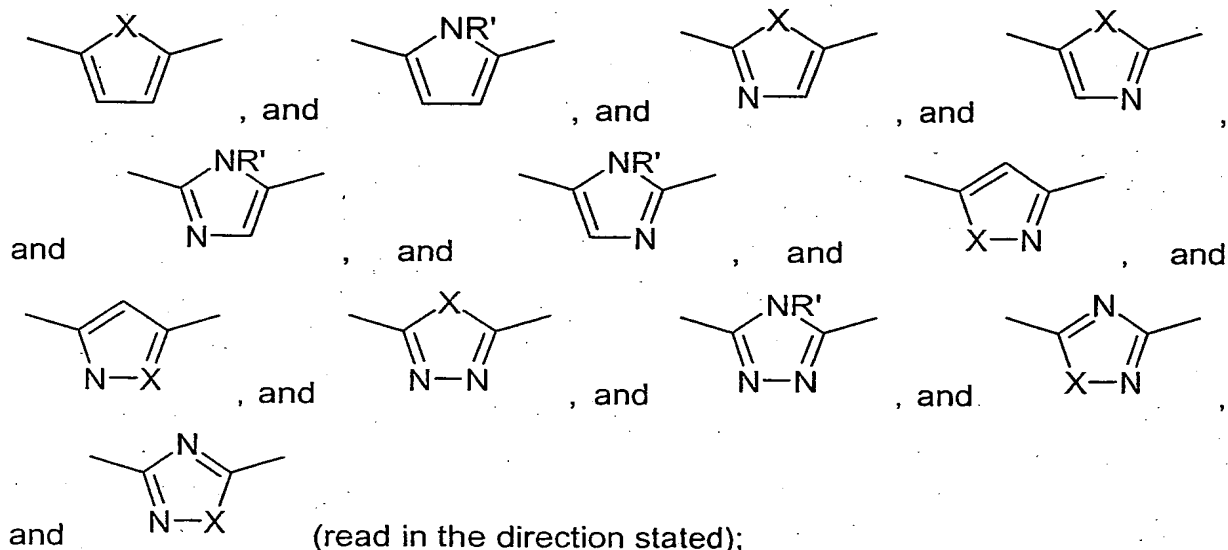
provided however,

if A represents 2,5-pyridyl or 3,6-pyridazinyl,
then B is not phenyl or substituted phenyl.

35

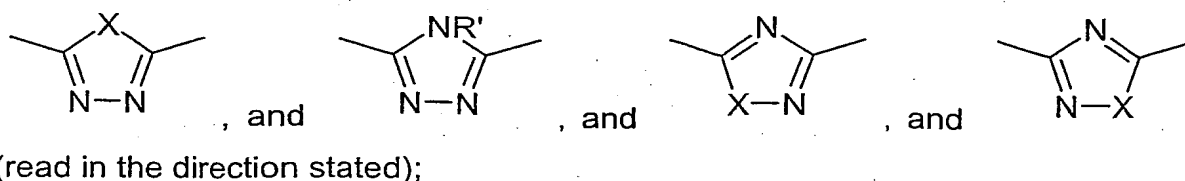
2. The diazabicyclic biaryl derivative derivative of claim 1, wherein R represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl.

3. The diazabicyclic biaryl derivative of either of claims 1-2, wherein A represents *m*-phenylene or *p*-phenylene, which phenylene group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro.
4. The diazabicyclic biaryl derivative of either of claims 1-2, wherein A represents a 5-membered aromatic monocyclic heterocyclic group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro.
5. The diazabicyclic biaryl derivative of claim 4, wherein the 5-membered aromatic monocyclic heterocyclic group is selected from



wherein X represents O, S or Se; and
R' represents hydrogen or alkyl.

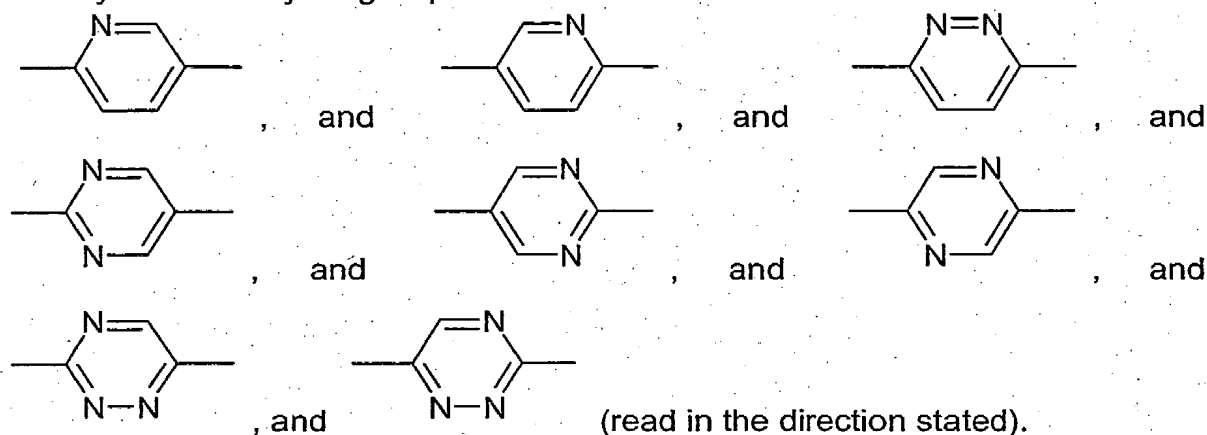
6. The diazabicyclic biaryl derivative of claim 5, wherein the 5-membered aromatic monocyclic heterocyclic group is selected from



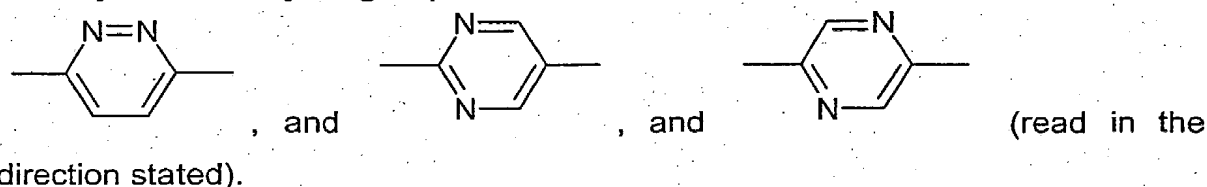
wherein X represents O or S; and
R' represents hydrogen or alkyl.

7. The diazabicyclic biaryl derivative of either of claims 1-2, wherein A represents a 6-membered aromatic monocyclic heterocyclic group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro.

8. The diazabicyclic biaryl derivative of claim 7, wherein the 6-membered aromatic monocyclic heterocyclic group is selected from



9. The diazabicyclic biaryl derivative of claim 8, wherein the 6-membered aromatic monocyclic heterocyclic group is selected from



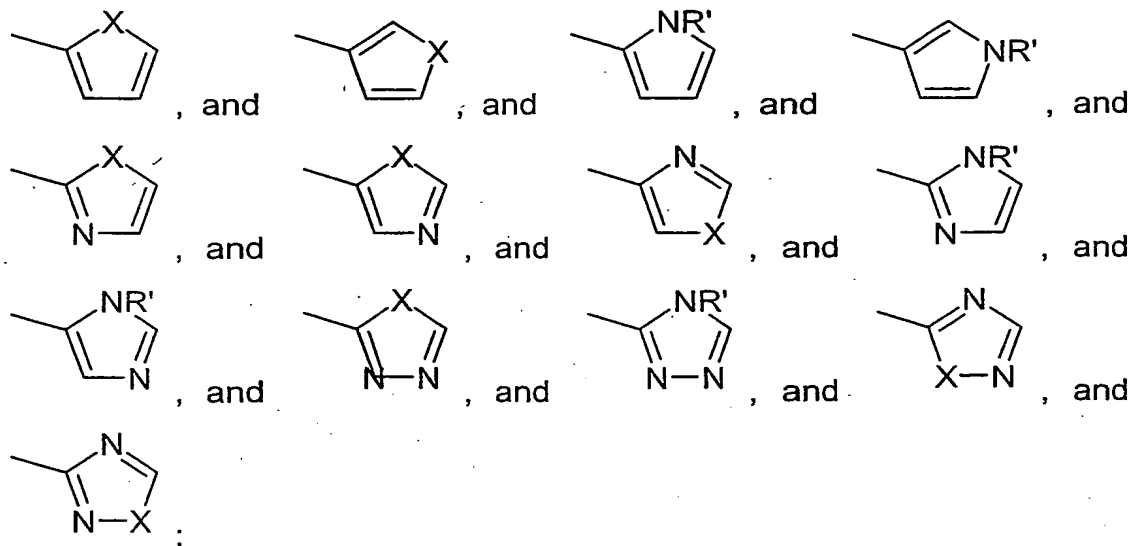
10. The diazabicyclic biaryl derivative of any of claims 1-9, wherein B represents a phenyl or naphthyl group, which aryl group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro.

11. The diazabicyclic biaryl derivative of any of claims 1-9, wherein B represents a 5- or 6-membered aromatic monocyclic heterocyclic group, which aromatic group may optionally be substituted one or more times with substituents selected from

the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro.

12. The diazabicyclic biaryl derivative of claim 11, wherein

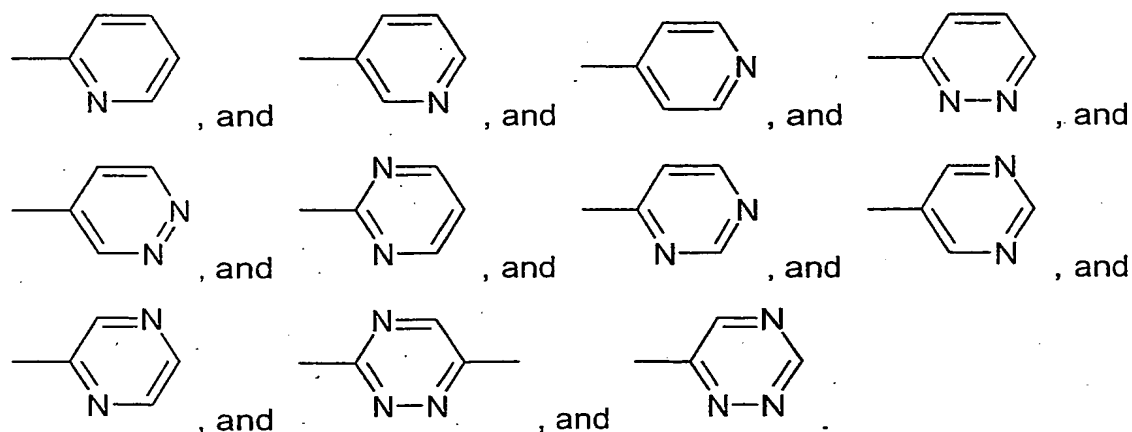
5 the 5-membered aromatic monocyclic heterocyclic group is selected from



wherein X represents O, S or Se;

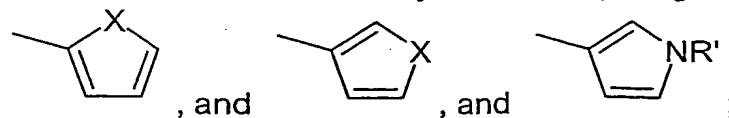
R' represents hydrogen or alkyl; and

the 6-membered aromatic monocyclic heterocyclic group is selected from



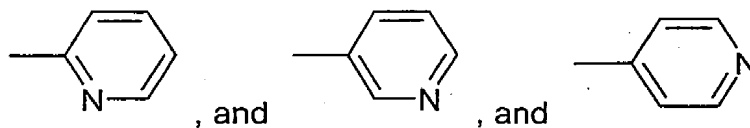
13. The diazabicyclic biaryl derivative of claim 12, wherein

the 5-membered aromatic monocyclic heterocyclic group is selected from



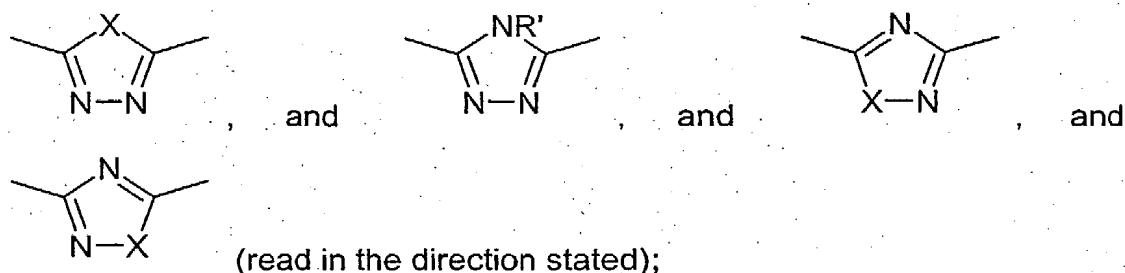
wherein X represents O or S;

R' represents hydrogen or alkyl; and
the 6-membered aromatic monocyclic heterocyclic group is selected from



5 14. The diazabicyclic biaryl derivative of either of claims 1-2, wherein

A represents a 5-membered aromatic monocyclic heterocyclic group is selected from

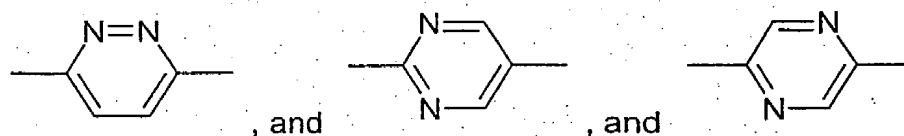


wherein X represents O or S;

R' represents hydrogen or alkyl;

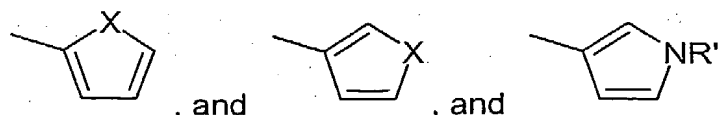
which aromatic group is optionally substituted with a substituent selected from the group consisting of halogen, CF₃, CN, amino and nitro; or

15 A represents a 6-membered aromatic monocyclic heterocyclic group is selected from



(read in the direction stated); which aromatic group is optionally substituted with a substituent selected from the group consisting of halogen, CF₃, CN, amino and nitro; and

B represents a 5-membered aromatic monocyclic heterocyclic group selected from



wherein X represents O or S; and

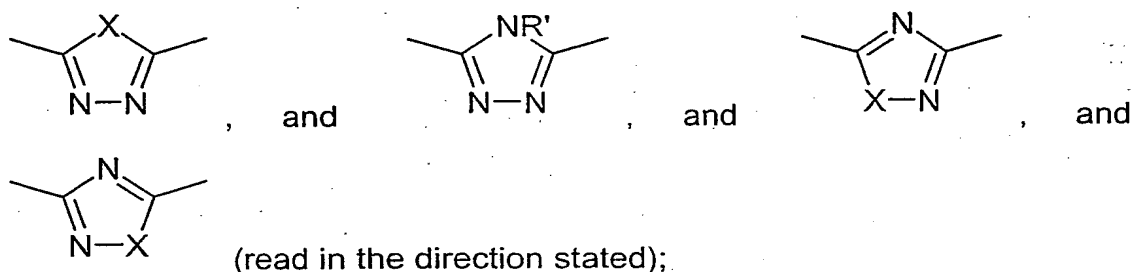
R' represents hydrogen or methyl;

which aromatic group may optionally be substituted one or two times with substituents selected from the group consisting of halogen, CF₃, CN, amino and nitro.

15. The diazabicyclic biaryl derivative of claim 14, which is
 2-[6-(3-Thienyl)-3-pyridazinyl]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;
 5-Methyl-2-[6-(3-thienyl)-3-pyridazinyl]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;
 or
 2-[6-(3-Thienyl)-2-pyrazinyl]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;
 or an enantiomer or a mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

16. The diazabicyclic biaryl derivative of either of claims 1-2, wherein

- A represents a 5-membered aromatic monocyclic heterocyclic group is selected from

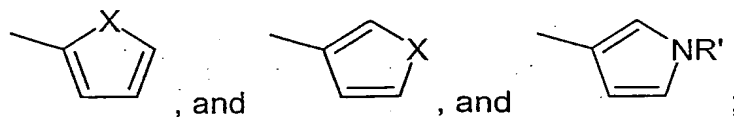


wherein X represents O or S;

R' represents hydrogen or alkyl; and

B represents a phenyl or naphthyl group; which phenyl or naphthyl group may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cyanoalkyl, halogen, CF₃, OCF₃, CN, amino and nitro; or

B represents a 5-membered aromatic monocyclic heterocyclic group selected from



wherein X represents O or S; and

R' represents hydrogen or methyl;

which aromatic group may optionally be substituted one or two times with substituents selected from the group consisting of halogen, CF₃, CN, amino and nitro.

17. The diazabicyclic biaryl derivative of claim 16, which is
2-[2-(-5-Phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;
2-[5-(-3-Phenyl-1,2,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-heptane;
5-Methyl-2-[2-(-5-phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-
5 heptane;
5-Methyl-2-[5-(-3-phenyl-1,2,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-
heptane; or
5,5-Dimethyl-2-[2-(-5-phenyl-1,3,4-thiadiazolyl)]-(1S,4S)-2,5-diazabicyclo-[2.2.1]-
heptane;
10 or an enantiomer or a mixture of its enantiomers, or a pharmaceutically
acceptable salt thereof.
18. A pharmaceutical composition comprising a therapeutically effective amount of a
diazabicyclic biaryl derivative of any of claims 1-17, or a pharmaceutically-
15 acceptable addition salt thereof, together with at least one pharmaceutically-
acceptable carrier or diluent.
19. Use of a diazabicyclic biaryl derivative of any of claims 1-18, or a
pharmaceutically-acceptable addition salt thereof, for the manufacture of a
20 pharmaceutical composition/medicament for the treatment, prevention or
alleviation of a disease or a disorder or a condition of a mammal, including a
human, which disease, disorder or condition is responsive to modulation of
cholinergic receptors and/or monoamine receptors.
- 25 20. The use according to claim 19, wherein the disease, disorder or condition relates
to the central nervous system.
21. The use according to claim 20, wherein the disease, disorder or condition is
anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction,
30 Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder
(ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral
Sclerosis, Gilles de la Tourette's syndrome, psychosis, depression, mania, manic
depression, schizophrenia, obsessive compulsive disorders (OCD), panic
disorders, eating disorders such as anorexia nervosa, bulimia and obesity,
35 narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy,
autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-
traumatic syndrome, social phobia, sleeping disorders, pseudodementia,
Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome,
chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

22. The use according to claim 19, wherein the disease, disorder or condition are associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.
23. The use according to claim 19, wherein the disease, disorder or condition is related to the endocrine system, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.
24. The use according to claim 19, wherein the disease, disorder or condition is a neurodegenerative disorders, including transient anoxia and induced neurodegeneration.
25. The use according to claim 19, wherein the disease, disorder or condition is an inflammatory disorder, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.
26. The use according to claim 19, wherein the disease, disorder or condition is mild, moderate or even severe pain of acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb pain, neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.
27. The use according to claim 19, wherein the disease, disorder or condition is associated with withdrawal symptoms caused by termination of use of addictive substances, including nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.
28. A method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a diazabicyclic biaryl derivative of any of claims 1-18.

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(25) Filing Language: English

(26) Publication Language: English

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- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations of inventorship (Rule 4.17(iv)) for US only

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(71) Applicant (for all designated States except US): NEUROSEARCH A/S [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PETERS, Dan [SE/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). OLSEN, Gunnar, M. [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). NIELSEN, Elsebet, Østergaard [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). JØRGENSEN, Tino, Dyhring [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). AHRING, Philip, K. [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(74) Common Representative: NEUROSEARCH A/S; Att: Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).

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(88) Date of publication of the international search report:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL DIAZABICYCLIC BIARYL DERIVATIVES

(57) Abstract: This invention relates to novel diazabicyclic biaryl derivatives, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors and modulators of the monoamine receptors and transporters. Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

WO 2003/094831 A3

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/ 03/00295

A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 44755 A (ABBOTT LAB) 3 August 2000 (2000-08-03) claim 11	1-28
X	WO 01 90109 A (DULL GARY MAURICE ; MILLER CRAIG HARRISON (US); TARGACEPT INC (US);) 29 November 2001 (2001-11-29) claims	1-28
X	WO 00 34284 A (SANOFI SYNTHELABO ; JEUNESSE JEAN (FR); NEDELEC ALAIN (FR); EVEN LU) 15 June 2000 (2000-06-15) claims	1-28
X	US 5 478 939 A (TRYBULSKI EUGENE ET AL) 26 December 1995 (1995-12-26) the whole document	1-28

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

23 October 2003

Date of mailing of the international search report

14 11 2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

GÓMEZ LAGERLÖF /EÖ

INTERNATIONAL SEARCH REPORT

International Application No.
CT/DK 03/00295**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 28
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 28

Claims 28 relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

nation on patent family members

International Application No.

PCT/ 03/00295

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